

REMARKS

Claims 1, 4, 7, and 9-24 are pending in the application. Claim 8 has been cancelled without prejudice. Claims 9 and 10 have been amended to depend from independent claim 1. These amendments add no new matter.

35 U.S.C. §112, 1st Paragraph (Written Description)

At page 2-5 of the Office Action, the Examiner finally rejected claim 8 as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claim 8 has been cancelled without prejudice, thereby obviating the present rejection.

35 U.S.C. § 112, 1st Paragraph (Enablement)

At pages 5-9 of the Office Action, the Examiner finally rejected claim 8 as allegedly not enabled. Claim 8 has been cancelled without prejudice, thereby obviating the present rejection.

35 U.S.C. §103(a) (Obviousness)

At pages 9-15 of the Office Action, the Examiner finally rejected claims 1, 4, 7, 8-10, 15, 17-19, and 22-24 as allegedly unpatentable over Smith et al. (1998) *J. Exp. Med.* 188:17-27 (“Smith) in view of Huston et al. U.S. Patent No. 5,013,653 (“Huston”) and Tudyka et al. (1997) *Protein Science*, 6:2180-87 (“Tudyka”).

Independent claim 1 is directed to a nucleic acid containing a nucleic acid sequence that encodes a fusion protein consisting of: (i) a signal peptide; (ii) a soluble form of human SSAO consisting of amino acids 29 to 763 of SEQ ID NO:2 or a fragment thereof exhibiting benzylamine oxidase activity; (iii) a fusion partner that enables dimerization of the soluble SSAO; (iv) a protease cleavage site; and (v) optionally one or more spacer amino acids sequences.

The Office Action contains the following statements regarding the disclosure of Smith:

- “Art and the specification teach that the soluble form of SSAO lacks the membrane spanning portion of the wild-type SSAO.” (Office Action at page 10)
- “[I]t would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a polynucleotide encoding a fusion protein comprising … a soluble form of SSAO of Smith” (Office Action at page 12)
- “Smith et al. teaches that the soluble form of SSAO lacks the membrane spanning portion of the wild-type SSAO.” (Office Action at page 13)

In addition, the Office Action states that

Smith et al. teaches expression and purification of a copper-containing amine oxidase, at least one year prior to the filing of the instant application. Therefore, coupled with the teachings of Smith et al. and the cited references, one having ordinary skill in the art would have had a reasonable expectation of success in expressing and purifying SSAO and soluble SSAO.

Applicants respectfully traverse the rejection in view of the following comments.

Smith describes the cloning of SSAO and expression of the recombinant protein on the surface of Chinese hamster ovary (CHO) cells. Smith states that SSAO is a membrane bound protein (see, e.g., Smith at page 25, right column). Smith contains no description whatsoever of a soluble form of SSAO. Applicants respectfully contest the passages from the Office Action reproduced above insofar as they may suggest that Smith describes a soluble form of SSAO.

Smith describes recombinant expression of full length, membrane-bound SSAO on the surface of CHO cells. Nowhere does Smith describe purification of this recombinant, non-soluble form of SSAO. Instead, when performing enzyme assays intended to measure amine oxidase activity of the recombinant protein, Smith uses lysates from CHO cells expressing recombinant membrane-bound SSAO (see, e.g., Smith at page 18, right column). No purification of any recombinant form of SSAO is described by Smith.

Smith describes the immunopurification of membrane-bound tissue-derived SSAO in quantities sufficient to obtain peptide sequences to assist in the cloning of the SSAO cDNA. However, Smith states that “[i]t was not possible to measure specific activities due to the very low yield of tonsillar VAP-1 protein obtained” (Smith at page 23, right column).

As detailed in the response to the previous office action, applicants submit that the claimed nucleic acid provides a solution to the long-felt but unsatisfied need of a means for

purifying to homogeneity and in high amounts a recombinant human soluble SSAO. The claimed nucleic acid permits the recombinant production of milligram quantities of pure, soluble, and biologically active human SSAO. Objective evidence that an invention fulfills a need that existed in the art for a long period of time without solution must be considered when assessing obviousness under 35 U.S.C. §103 (see, e.g., MPEP §716.04, I).

As detailed above, Smith contains no disclosure of a soluble form of SSAO or the purification of any recombinant form of SSAO. In addition, Smith clearly states that its techniques for purifying native, membrane-bound SSAO from tissue lysates were deficient in terms of the yield of protein obtained.

As further evidence of the long-felt but unsatisfied need of a means for purifying high amounts a recombinant human soluble SSAO, Holt et al. (1998) *Biochemistry*, 37:4946-57 (enclosed with the previous response as "Exhibit C") and Elmore et al. (2002) *J. Biol. Inorg. Chem.* 7:565-79 (enclosed with the previous response as "Exhibit D") both recognized the desirability of obtaining high yields and a homogeneous supply of a mammalian copper-containing amine oxidase such as SSAO (see, e.g., Exhibit C in its Abstract stating "the identity of the quinone cofactor and the presence of copper remain unconfirmed, and SSAO has proved impossible to purify to homogeneity in sufficient yield to permit cofactor identification" (emphasis added); see also Exhibit D at page 567, left column, lines 8-18). In addition, Exhibit D (which was published approximately six years after the publication in 1996 of the cloning of human SSAO) noted that the heterologous overexpression and purification of recombinant human diamine oxidase described therein was "the first successful overexpression of any mammalian copper-containing amine oxidase"¹ (see Exhibit D in its Abstract and page 567, left column, lines 10-13; emphasis added). Further underscoring the difficulty that persons of skill in the art had experienced in expressing and purifying copper-containing amine oxidases (long after publications reporting the cloning of cDNAs encoding such proteins), Exhibit D referred to the then-recent overexpression of a copper amine oxidase from a plant species as a "notable accomplishment" (Exhibit D at page 574, left column).

¹ SSAO is a mammalian copper-containing amine oxidase.

In view of the foregoing, Exhibits C and D clearly establish that despite the desire of those of skill in the art, no soluble mammalian copper-containing amine oxidase had been expressed recombinantly and purified prior to the present application. Exhibits C and D thus provide objective evidence that (i) there was a long-felt need in the art for a means of producing soluble recombinant human SSAO, and (ii) this long-felt need was not fulfilled prior to the filing of the present application.

The specification describes the successful expression and purification of a secreted fusion protein encoded by the claimed nucleic acid (see, e.g., page 15, line 20, to page 16, line 18). The fusion protein was secreted from mammalian cells transfected with the claimed nucleic acid and was purified directly from the culture medium by glutathione-affinity chromatography (see, e.g., page 16, lines 20-30). By specific proteolysis, the fusion partner (GST) and the protease were removed, providing a high yield (milligram quantities) of pure, soluble, and highly active recombinant human SSAO protein (see, e.g., page 17, line 1 to page 19, line 3), thereby satisfying the long-felt need recognized in the art.

In view of the foregoing, applicants respectfully submit that the cited references do not render the claimed invention obvious and therefore request that the Examiner withdraw the rejection.

At pages 15-17 of the Office Action, the Examiner rejected dependent claim 11 as allegedly unpatentable over Smith in view of Huston, Tudyka, and Zambidis et al. (1996) *Proc. Natl. Acad. Sci. USA* 93:5019-24 (“Zambidis”). Zambidis was cited only for its disclosure of a mouse IgG1 heavy chain signal peptide and thus does not cure the deficiencies in Smith, Huston, and Tudyka detailed above with respect to independent claim 1. As a result, the combination of references do not render obvious the nucleic acid of dependent claim 11.

At pages 17-20 of the Office Action, the Examiner rejected dependent claims 12, 13, 20, and 21 as allegedly unpatentable over Smith in view of Huston, Tudyka, and Brenda Enzyme Database, EC 3.4.22.28 (“Brenda”). Brenda was cited only for its disclosure of 3C protease amino acid sequences and thus does not cure the deficiencies in Smith, Huston, and Tudyka

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detailed above with respect to independent claim 1. As a result, the combination of references do not render obvious the nucleic acid of dependent claims 12, 13, 20, and 21.

CONCLUSIONS

Applicants ask that all claims be allowed in view of the amendments and remarks contained herein.

Enclosed is a Petition for a Three Month Extension of Time and a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 13425-053001.

Respectfully submitted,

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